Remarks

Claims 12-19 and 37-52 were previously pending in this application. Claim 12 has been amended. Support for this amendment can be found in the specification at least on page 72 lines 21-22 and in claim 18 as originally filed. Claims 18, 19 and 37 have been cancelled. Claims 12-17 and 38-52 are now pending with claim 12 being an independent claim. Claims 12-17, 38-40, 42, 44, 45, 47, 48 and 52 are currently under review.

No new matter has been added.

Restriction Requirement

Claims 41, 43, 46 and 49-51 are currently withdrawn based on a species election. Upon allowability of the generic claim (claim 12), examination of these withdrawn claims is requested.

Rejection under 35 U.S.C. § 112, second paragraph

Claims 12-18, 38-40, 42, 44, 45, 47, 48 and 52 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Claim 18 is now cancelled.

The Examiner states that the claims are vague with respect to prevention of allergic asthma in a hypo-responsive subject. The Examiner states that if a subject has previously been treated with an asthma or allergy medicament then the subject already has allergic asthma, and therefore it is unclear how the claimed invention can be used for prevention. Without conceding the Examiner's position, Applicant has amended claim 12 to read "treating or preventing an allergic asthmatic event." Support for this amendment can be found in the instant specification on page 72 lines 21-22, which states that the method of the invention can be used "in anticipation of an asthmatic or allergic event in order to prevent an asthmatic or allergic event". The specification describes asthma as a chronic condition (page 1 line 13), and that "[a]sthma patients take the long-term control medications on a daily basis to achieve and maintain control of persistent asthma" (page 2 lines 1-2). The specification defines a "hypo-responsive subject" as "one who has previously failed to respond to a treatment directed at treating or preventing asthma or allergy or one who is at risk of not responding to such a treatment" (page 47 lines 6-8). Therefore, the claimed method can be used to prevent future asthmatic events in a patient with chronic allergic asthma.

In view of the foregoing, the method of claim 12 for treating or preventing an allergic asthmatic event, has definite meaning as provided by the specification. Therefore claims 12-17, 38-40, 42, 44, 45, 47, 48 and 52 meet the conditions set forth in 35 U.S.C. § 112, second paragraph, and reconsideration and withdrawal of the rejection is respectfully requested.

Rejection under 35 U.S.C. §112, first paragraph

Claims 12-18, 38-40, 42, 44, 45, 47, 48 and 52 are rejected under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. Claim 18 is now cancelled.

The test of enablement is whether undue or unreasonable experimentation is required for one of ordinary skill in the art to practice (i.e., make and use) the claimed invention. Thus, based on the specification and the knowledge in the art at the time of filing (i.e., effective filing date), one of ordinary skill must be able to make and use the claimed invention without undue experimentation. The experimentation may be complex and still not undue, if the art routinely engages in that level of experimentation. The factors to be considered in determining whether undue experimentation is required include 1) the nature of the invention; 2) the breadth of the claims; 3) the state of the art; 4) the level of ordinary skill in the art; 5) the level of predictability in the art; 6) the amount of direction provided by the inventor(s); 7) the existence of working examples; and 8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. In re Wands, 858 F.2d 731; 8 USPQ 2d 1400 (Fed. Cir. 1988). These factors are to be considered in their totality with no one factor being dispositive of the issue of enablement.

Nature of the invention and breadth of the claims: The invention relates in part to the use of immunostimulatory nucleic acids, such as CpG ODN, for preventing or treating allergy and/or asthma in hypo-responsive subjects. The claims relate to a method of preventing or treating allergic asthma in a hypo-responsive subject using immunostimulatory nucleic acids.

Level of ordinary skill in the art: The level of ordinary skill in the art is high. Ordinary artisans would include medical practitioners who treat allergic asthma using any of a number of treatment modalities known in the art at the time of filing. A high level of ordinary skill in the art lessens the amount of direction to be provided by the inventor(s) since one of ordinary skill will be accustomed to the experimentation required to practice the claimed invention.

State of the art and level of predictability in the art: The Examiner cites a number of references to support her assertion that the state of the art of allergic asthma treatment using CpG nucleic acids was unpredictable at the time of filing.

Several references have been cited by the Examiner to support her position that the art is unpredictable with regards to the efficacy or safety of using CpG nucleic acids to treat allergic asthma in humans. Applicant stresses however that human testing, which is the domain of the FDA and not the USPTO, is beyond the enablement standard required for, and thus should not be a bar, to patentability. In re Brana, 51 F.3d 1560 (Fed. Cir. 1995).

Dziadzio et al. (Handbook of Experimental Pharmacology 161:273-285, 2004) and Metzger et al. (J. Allergy. Clin. Immunol. (104)2 Pt. 1:260-266, 1999) are both cited for the teaching that CpG ODN therapy has yet to be demonstrated in human clinical trials. Both references however summarize effects of CpG ODN, in in vitro and in vivo murine systems, that parallel those required for human therapy. Neither reference doubts that CpG ODN will be effective in humans. Dziadzio et al. actually teaches that CpG ODN are encouraging as potential therapies for allergic disease. After summarizing several sets of data on page 280, the reference teaches:

> "These data suggest that ISS-ODN can induce a Th1 phenotype prior to allergen exposure. It appears that even without the presence of allergen, CpG motifs can induce a Th1 phenotype in multiple cell types including B cells, antigen-presenting cells (macrophages, dendritic cells), T cells, and NK cells. The expression of Th1 cytokines along with an upregulation of costimulatory molecules on these cells underscores the importance of ISS-ODN in Th1 and innate immune responses. The persistence of a Th1 response after antigen challenge in sensitized mice is encouraging as potential therapy for allergic disease." (page 280, 2nd-3rd full paragraphs).

The reference as a whole therefore does not support a finding that the claimed invention was unpredictable at the time of filing of the patent application.

Several Phase I and II studies involving CpG ODN have been performed in humans to date. These studies demonstrate that CpG ODN are well tolerated in human subjects. (See for example Creticos et al. Immunotherapy with immunostimulatory oligonucleotides linked to purified ragweed Amb a 1 allergen: effects on antibody production, nasal allergen provocation, and ragweed seasonal rhinitis. J Allergy Clin. Immunol. 109(4), 742-743. 2002; Simons et al. Selective immune redirection in humans with ragweed allergy by injecting Amb a 1 linked to

immunostimulatory DNA. J Allergy Clin Immunol 113, 1144-1151 (2004); Krieg et al. Induction of systemic TH1-like innate immunity in normal volunteers following subcutaneous but not intravenous administration of CPG 7909, a synthetic B-class CpG oligodeoxynucleotide TLR9 agonist. J Immunother. 27, 460-471 (2004); Cooper et al. CpG 7909, an immunostimulatory TLR9 agonist oligodeoxynucleotide, as adjuvant to Engerix-B HBV vaccine in healthy adults: A double-blind Phase I/II study. J Clin. Immunol 24, 693-702 (2004); Halperin et al. A phase I study of the safety and immunogenicity of recombinant hepatitis B surface antigen co-administered with an immunostimulatory phosphorothioate oligonucleotide adjuvant. Vaccine 21, 2461-2467 (2003); Siegrist et al. Co-administration of CpG oligonucleotides enhances the late affinity maturation process of human anti-hepatitis B vaccine response. Vaccine 23, 615-622 (2004); Cooper et al. Safety and Immunogenicity of CpG 7909 Injection as an Adjuvant to Fluarix Influenza Vaccine. Vaccine 22, 3136-3143 (2004); Speiser et al. Rapid and strong human CD8(+) T cell responses to vaccination with peptide, IFA, and CpG oligodeoxynucleotide 7909. J Clin. Invest 115, 739-746 (2005); van Ojik et al. Phase I/II study with CpG 7909 as adjuvant to vaccination with MAGA-3 protein in patients with MAGE-3 positive tumors. Ann. Oncol. 13, 157. 2003.)

McCluskie et al. (1999) Molecular Medicine 5:287-300 (in particular page 296) is cited for the proposition that "biological responses to the administration of CpG containing oligonucleotides vary ... depending on the mode of administration and the organism." McCluskie et al. is an article describing DNA vaccines (i.e., vaccines in which an antigen or other protein is encoded by a plasmid or other nucleic acid vector) against Hepatitis B virus. The reference teaches that the response to the DNA vaccine varies according to the mode of delivery and the organism. The presence of CpG motifs in the DNA vaccine can influence the Th bias of the induced response. (See page 296.) The claimed invention relates to CpG oligonucleotides. The issues of predictability and therapeutic efficacy are different for CpG ODN and DNA vaccines. Accordingly, the teachings of McCluskie et al. are not relevant to the claimed invention.

Krieg et al. (2000) Immunology Today 21:521-526 is cited for the same proposition. The Examiner pointed specifically to page 524, however the only passage on page 524 related to this proposition is the teaching that the "magnitude of cytokine response to CpG is much greater in mouse cells than in human or monkey cells". This passage refers to potential side effects

induced by CpG. It is correctly interpreted to mean the likelihood and severity of side effects such as SIRS are expected *to be less in humans than in mice*. Such disparity is clinically beneficial.

The reference further teaches on page 524 that "studies have shown CpG ODN ... to be effective with multiple types of antigens and routes of immunization, including mucosal immunization", and that "[u]nlike many vaccine adjuvants that have been extremely effective in mice but disappointing in humans, CpG DNA is also highly effective in higher primates." These teachings support the consistency of an induced response in different organisms and using different administration routes.

The reference further teaches the usefulness of CpG oligonucleotides in producing a Th1 biased immune response. Page 524 includes the following teaching:

> "The potent Th1 adjuvant effect of CpG can even override preexisting Th2 immune responses; it has been used as an adjuvant for allergy vaccines, where it induces Th1 responses to antigens in the presence of a preexisting Th2 response, leading to decreased symptoms following subsequent allergen inhalation. CpG DNA has been shown to have similar Th1-inducing effects on cells from allergic humans in vitro, and clinical trials of CpG DNA as an asthma therapeutic are currently under way. It should be stressed that CpG DNA is effective in asthma immunotherapy even when given as a stand-alone agent without allergen ..."

Therefore, the teachings of Krieg et al. support rather than refute the use of CpG ODN in immunotherapy treatment for asthma.

Wohlleben et al. (2001) Trends in Immunology 22:618-626 is cited for the teaching that "all approaches that induce Th1 responses have the potential side effects of Th1-mediated inflammation, potentially causing serious tissue damage." However, when taken as a whole, Wohlleben et al. describes administration of CpG ODN for asthma and allergy as a promising therapy and thus support the use of CpG ODN for treating allergic asthma. In the abstract, Wohlleben et al. states "[t]he most promising approaches include the induction of ... Th1 immune responses, through the use of killed bacteria ... CpG oligodeoxynucleotides, or plasmid DNA." Wohlleben et al. characterizes vaccines "that combine reagents that induce strong Th1 responses with defined allergens" as promising therapies. (See page 618 column 2 and page 619 column 1.) CpG ODN would be one such reagent. Wohlleben et al. further states that one of the most promising candidates for atopic disorders is CpG ODN therapy.

Further, the teachings of Wohlleben et al. with respect to potential side effects do not support a lack of enablement of the claims. Wohlleben et al. teaches on page 620 immediately following the discussion of side effects that "it is totally unclear if this can also occur in healthy rodents or, more importantly, humans." (See page 620 second column first paragraph.)

Satoh et al. (2002) Fukushima Igaku Zasshi 52:237-250 is also cited in order to demonstrate that CpG is associated with dangerous side effects. The Satoh et al. reference is an abstract describing a study in which CpG oligonucleotides are administered subcutaneously to mice in combination with DNFB treatment in an experimental model system for allergic contact dermatitis. The abstract concludes that "CpG ODN vaccination may elicit and aggravate side effects such as harmful $CD8^+$ T cell-mediated type IV hypersensitivity response". The teachings of Satoh et al. however are not sufficient to establish a lack of enablement for the claimed invention. The ACD is caused by DNFB treatment. The fact that CpG oligonucleotides may contribute to type IV hypersensitivity responses initiated by DNFB does not establish that CpG oligonucleotides would cause ACD in the absence of DNFB. Moreover, subcutaneous administration of CpG ODN, like that in Satoh et al., has been performed in humans for a cancer trial, as described in Kim et al. (2004) Blood 4:11, abstract # 743 (attached). Toxic effects that would halt further human trials were not observed, even though the patients were provided CpG oligonucleotides in very aggressive doses. The Kim et al. abstract concludes that "weekly doses up to 0.36 mg/kg have been well tolerated". Accordingly, the predictions of Satoh et al. based on murine models have not been observed in human trials.

Applicant further notes that the issue of whether a drug is safe and has no side effects in not an appropriate test for enablement. MPEP2164.01(c). "The applicant need not demonstrate that the invention is completely safe." In fact, one cannot possibly determine the parameters of safety without a controlled clinical trial, and it is well established that a clinical trial is not required for enablement.

Kline et al. (2002) Am. J. Physiol. Lung Cell Mol Physiol., 283:L170-L179 is cited as teaching that "a single treatment of CpG-ODN alone was ineffective in reducing the manifestations consistent with asthma" in the animal model. As stated above, CpG ODN therapy in allergic asthma is optimized for dose and mode and frequency of administration during human testing. Doses are within the purview of those skilled in the art, and the data in the paper support that monotherapy at appropriate doses can work. More importantly, as the Examiner

acknowledged, the reference teaches that while "splenocytes from OVA-treated mice" (i.e., the non-CpG control) "did not develop an antigen-specific Th1 phenotype ... mice treated with CpG ODN and OVA had a marked shift toward a Th1 response to antigen as well as reduction in airway eosinophilia, serum IgE and broncheal hyperreactivity." The referenced passages teach that CpG ODN treatment is effective in eliciting a Th1 immune response for treatment of allergic asthma and therefore are consistent with the claimed method.

Kline et al. (1998) J. Immunol. 160:2555-2559 is also cited by the Examiner. The reference however supports the predictability of CpG therapy in asthma. For example, on page 2555 column 2, the reference states "during childhood, repeated Ag exposures in the presence of CpG DNA may bias immune responses to Th1 and protect against Th2 type responses such as asthma". The reference abstract states that in a previously sensitized mouse, CpG ODN can prevent allergen-induced airway inflammation. These studies teach that exposure to CpG DNA is protective against asthma and therefore they support the claimed method.

Weiner et al. (2000) J. Leukocyte Biology 68:456-463 is cited for the proposition that the molecular mechanism of CpG is unknown. Knowledge of the mechanism is not a prerequisite for patentability. Newman v. Quigg, 877 F.2d 1575, 1581, 11 USPQ2d 1340, 1345 (Fed. Cir. 1989). At the time of filing, the cellular effects of CpG oligonucleotides were known. Table 1 of the reference lists examples of cellular effects arising from immunostimulatory CpG ODN. A lack of understanding of the molecular mechanism does not render the cellular results unpredictable. Other statements in Weiner are consistent with enablement of the claimed invention. For instance it is taught on page 456 1st column second full paragraph that "studies to date suggest CpG DNA could have significant therapeutic promise in the treatment of a variety of disorders, including infectious disease, allergy, and cancer." Page 457 under "In vivo effects of CpG ODN" teaches that "extensive studies have been done in rodents, and some studies have been done in non-human primates. The observed in vivo data fit well with the in vitro data outlined above."

Agrawal et al. (2000) Molecular Medicine Today 6:72-81 is cited for the proposition that the effect of "the incorporation and positioning of chemical modifications relative to the CpG dinucleotide are highly unpredictable." Agrawal et al. is an article summarizing antisense oligonucleotide therapy. The reference suggests that in order to reduce non-antisense related activity of antisense ODN, CpG motifs should be avoided or at least mutated to their methyl

forms. (See page 78.) The instant specification teaches that a CpG containing oligonucleotide has an unmethylated C in the CpG motif. The reference therefore stands for the proposition that CpG motifs are immunostimulatory.

Amount of direction provided by the inventor: The Examiner states that the Applicant has not provided sufficient guidance to allow one of skill in the art to practice the claimed invention. The Examiner states that one skilled in the art would not be able to practice the claimed invention in view of the alleged "lack of guidance in the specification and the known unpredictability associated with the ability to predict the biological effects exerted by CpG containing oligonucleotides in a hypo-responsive subject." Applicant respectfully disagrees. As discussed above, the state of the art was not unpredictable.

Furthermore, the specification provides guidance for the administration of immunostimulatory nucleic acids. Pages 71-72 of the specification provide detailed instruction regarding doses and ranges of doses, and timing of administration. Pages 76-79 teach various modes of administration. In addition, a skilled practitioner of the art would be aware that one likely route of administration for treatment of allergic asthma is one that delivers a therapeutic composition to the airways, e.g. aerosol delivery. Page 25 lines 22-24 of the specification reads "[m]ost of the asthma/allergy medicaments have been identified. These amounts can be adjusted when they are combined with immuno-stimulatory nucleic acids by routine experimentation." Administration of immunostimulatory nucleic acids to a hypo-responsive subject would be possible without undue experimentation using methods known in the art.

Working examples: The Examiner asserts that there are no working examples for the treatment of asthma or allergy in the specification in the form of in vitro assays, in vivo animal models, or in vivo examples. The courts have previously held that a specification need not contain a working example if the disclosure of the invention is adequate to allow one of ordinary skill to practice it without undue experimentation (i.e., if the disclosure is otherwise enabling). In re Borkowski, 422 F.2d 904, 164 USPQ 642 (CCPA 1970). As argued above, the instant disclosure meets this requirement.

The lack of a working example in the context of an enabling disclosure and predictability in the art is not a sufficient basis for an enablement rejection. In view of the totality of the factors discussed above, the lack of a working example, particularly the lack of an in vivo (e.g., in human) working example, does not preclude enablement of the present invention.

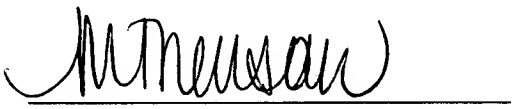
Quantity of experimentation: The quantity of experimentation needed to make and use the invention, in view of the disclosure and the state of the art at the time of filing, is not beyond the level of experimentation routinely practiced by persons of ordinary skill in the art.

In view of the foregoing, reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, second paragraph, is respectfully requested.

Conclusion

A Notice of Allowance is respectfully requested. If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825.

Respectfully submitted,



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x01.06.06x

[743] TLR9 Agonist Immunomodulator Treatment of Cutaneous T-Cell Lymphoma (CTCL) with CPG7909. Session Type: Oral Session

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CPG 7909 belongs to a new class of chemically defined CpG immunomodulators that target dendritic cell TLR9 receptors inducing IL-12, IFN-gamma, and NK cell function. The rate and durability of response to CPG 7909 was investigated in refractory patients with recurrent or advanced CTCL, who had failed one or more systemic therapies. Dose escalation with weekly sc dosing of patients at 0.08, 0.16, 0.24, or 0.28 mg/kg (3 patients/cohort) for 24 weeks is nearing completion. Additional patients continue to receive treatment at 0.32 (4 patients) or 0.36 mg/kg (12 patients). Clinical response, monitored by Composite Assessment of Index Lesion Disease Severity (CA) and Physician's Global Assessment of Clinical Condition, has been documented. Of 28 patients enrolled, 7 (25%) have achieved objective clinical response, 5 with partial response (PR) and 2 with complete response (CR). Eleven patients have maintained stable disease (SD), while 10 have had progressive disease (PD). Eight patients have completed 24 weeks of treatment (5 SD, 2 PR, 1 CR) with 12-16 weeks of response while on study. Six patients (3 SD, 2 PR,1 CR) are currently ongoing in the study. Three patients (2 PR, 1 SD) continue to receive long term CPG 7909 at 0.12 mg/kg (58 total doses), 0.28 mg/kg (34 total doses) or 0.32 mg/kg (29 total doses) in a follow on protocol. Responses have been maintained up to 46 weeks. Weekly doses up to 0.36 mg/kg have been well tolerated. Most reported adverse events have been of CTC grade 1 or 2. The most common are dose-related local injection site reactions (erythema, induration, edema, inflammation and pain) and mild or moderate flu-like symptoms (fatigue, rigors, fever, arthralgia). Four patients had CTC grade 3 drug related AEs: one decreased lymphocyte count (0.08 mg/kg), one increased gamma glutamyl transferase (0.16 mg/kg), one decreased absolute polys (0.36 mg/kg) and one fatigue (0.36 mg/kg). Enrollment in the phase II portion of the study is ongoing and compares results of patients randomized to receive either 10 mg or 25 mg sc weekly for 24 weeks (equating to effective doses seen in dose escalation).

Clinical Response with CPG 7909 - 16 M, 12 F

Dose	N	Disease Stage	CR	PR	SD	PD
0.36 mg/kg	12	IB (7), IIB, III (3), IVA	0	2	6	4

0.32 mg/kg	4	IIA, IIB, IVA (2)	1	0	1	2
0.28 mg/kg	3	IB (2), III	0	1	2	0
0.24 mg/kg	3	IB, IIB (2)	0	1	1	1
0.16 mg/kg	3	IB (2), IIA	1	1	1	0
0.08 mg/kg	3	IB (2), IVA	0	0	0	3
Total	28		7%	18%	39%	36%

Abstract #743 appears in Blood, Volume 104, issue 11, November 16, 2004
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Tuesday, December 7, 2004, 08:00 AM

Simultaneous Session: Lymphoma - Therapy with Biologic Agents (8:00 AM-10:00 AM)

[743] TLR9 Agonist Immunomodulator Treatment of Cutaneous T-Cell Lymphoma (CTCL) with CPG7909.
Session Type: Oral Session

Authors: Youn Kim, Michael Girardi, Madeline Duvic, Timothy Kuzel, Alain Rook, Brian Link, Lauren Pinter-Brown, Carol Comerci, Sonja McAuley, Tess Schmalbach

Date/Time: Tuesday, December 7, 2004 - 08:00 AM

Session Info: Simultaneous Session: Lymphoma - Therapy with Biologic Agents (8:00 AM-10:00 AM)